--8. The [method] use of Claim 5 [in which] wherein the glycolipid storage disease is Gaucher's disease. - -

--9. The [method] use as in any one of Claims 1-8, [in which] wherein the N-alkyl derivative of deoxynojirimycin is administered in a dose of from about 0.1 to about 1000 mg and the glucocerebrosidase is administered in a dose of about 7.5 to about 60 U per kilogram of weight of said patient in a pharmaceutically acceptable diluent or carrier. - -

a3

Please cancel Claims 10-13.

A clear copy of Claims 1-9 as thus amended by re-writing is attached hereto.

REMARKS

Claim Rejections – 35 USC § 112

Claims 1-9 and 11-13 have been rejected under 35 U.S.C. 112, second paragraph, as being vague and indefinite in recitation of the limitation "The method..." in Claim 1, line 1, and in a typographical error in Claim 7, line 2, in which the word "is" was misspelled as "in". Likewise, Claims 3-5 and 11-13 have been rejected for recitation of the abbreviation "DNJ", and Claims 2-9 and 11-13 have been rejected for recitation of the phrase "in which".

In accordance with the Examiner's requirements, Claim 1, line 1, is amended herewith to replace the term "The" with the term "A", and Claim 7, line 2, is amended to replace the term "in" with the term "is". Claim 1 is further amended herewith by inserting the abbreviation "DNJ" in parenthesis after the term "deoxynojirimycin", which is the first instance of its occurrence in the claims.

Claims 2-9 are amended by replacing the phrase "in which" with the term "wherein".

The rejections as applied to Claims 10-13 are now moot since these claims are cancelled herewith.

In view of the above amendments to the Claims, which comply with all of the Examiner's requirements, it is respectfully requested that the claim rejections under 35 U.S.C. § 112, second paragraph, be withdrawn.

Claim Rejections – 35 USC § 102

Claims 1-3, 6-7, and 10 and 11 have been rejected under 35 U.S.C. § 102(b) as being anticipated by *Aerts et al.* (WO 98/02161). It is noted that for support of this rejection the Examiner refers especially to Claim 16 and TABLE 3 on page 20 of *Aerts et al.*

This rejection is traversed for reasons as follows:

- First, Claims 10-13 have been cancelled, and the remaining Claims 1-9 have been amended, whereby they no longer recite a "method of treatment" with the combination of drugs but, instead, recite the "use" of the combination of drugs "for the preparation of a medicament". That is, the claims recite a method of preparation rather than a method of treatment. The claims thus have been amended to claim the invention as claimed in the allowed EP 1 196 190 B1, which is a National Filing of PCT/US/16340, of which the present U.S. application also is a National Filing.

- Secondly, Claim 16 and Claims 1-4, on which Claim 16 of *Aerts et al.* depends, do not disclose the N-alkyl derivatives of DNJ that are

recited in applicant's claims. Instead, the *Aerts et al.* claims define DNJ derivatives in which a large hydrophobic moiety is linked to the DNJ through a spacer which may be a $-(CH_2)_n-$ in which n = 3-8. The large hydrophobic moiety is exemplified by adamantanemethanol, cholesterol, β-cholesterol, adamantol, and 9-hydroxyphenanthrene. The spacer as defined by *Aerts et al.* does not have a terminal CH_3 such as in propyl, butyl or pentyl, etc., as in applicant's N-alkyl derivatives of DNJ, but consists, instead, of only an internal $-(CH_2)_n-$ link without a terminal CH_3. Thus, the respective DNJ derivatives of *Aerts et al.* and applicant are significantly different compounds. It is axiomatic that when the claimed invention is not identically disclosed in a reference, then the reference does not anticipate. *In re Bond*, 910 F.2d 831, 15 USPQ2d 1566, 1567, 1568 (Fed. Cir. 1990).

- Thirdly, TABLE 3 on page 30 of *Aerts et al.* does not show inhibition with N-alkyl derivatives of DNJ. Instead, the reference shows only "apparent Ki values" of these derivatives at 100 μM concentration in membrane suspensions. In TABLE 4 on page 31, which deals with inhibition, it is specifically stated that the N-alkyl derivatives of DNJ show "no significant inhibition" of glucocerebrosidase and relatively little inhibition of glucosylceramidase at various concentrations in Melanoma cells. There is no inherent teaching here of the preparation of a medicament with the two types of drugs as claimed by applicant.

At page 14, line 36, to page 15, line 7, *Aerts et al.* makes the following further statements concerning N-alkyl derivatives of DNJ:

> "...their specificity ... was poor"; they are "unattractive for administration to the already glucocerebrosidase-deficient Gaucher patients"; and they would "seriously interfere with enzyme therapy of patients due to their inhibitory effect on the administered aglucerase or imiglucerase."

Then, at page 15, lines 18-21, *Aerts et al.* characterizes these expected results as being "negative results" with the known glucosidase inhibitors. The reference thus teaches away from (contrary to) applicant's invention. The ordinary

person skilled in the art would not be motivated or induced to carry out applicant's invention based on any teaching found in *Aerts et al.*

- Fourthly, as amended herewith applicant's claims recite the preparation of a medicament for the alleviation or inhibition of a glycolipid storage disease. This alleviation or inhibition of the glycolipid storage disease contradicts, i.e., is the opposite of, the teaching of *Aerts et al.* which states that the specificity of the N-alkyl derivatives was "poor" and that they are "unattractive for administration" and constitute "negative results". Positive results are obtained by Aerts et al. only if the inhibitor contains the spacer with a large hydrophobic moiety. It is thus self-evident that *Aerts et al.* does not disclose the same subject matter claimed by applicant. That is, since *Aerts et al.* does not obtain the same results disclosed by applicant, the reference clearly lacks an element of applicant's claims. Under such circumstances there can be no anticipation. *Kloster Speedsteel AB v. Crucible Inc.*, 793 F2d 1565, 230 USPQ 81, 84 (Fed. Cir. 1986), *cert. denied*, 479 U.S. 1034 (1987). Further support for applicant's contention that *Aerts et al.* lacks an element of applicant's claim is provided in the next point.

- Fifthly, the *Aerts et al.* disclosure is directed to inhibition of a different enzyme than recited in applicant's claims. Thus, on the one hand, the *Aerts et al.* disclosure is directed to the "Design of a Specific Inhibitor for Glucosylceramidase" as seen from that heading in the middle of page 14. As specifically stated by *Aerts et al.* at page 14, lines 23-24, the purpose of their invention was "to identify a suitable inhibitor for the enzyme" thus denoted.

On the other hand, applicant's claims are directed to use of a different enzyme, namely "glucocerebrosidase."

These are two different enzymes. Glucocerebrosidase as recited in applicant's claims is a lysosomal β-glucosidase, and it is a deficiency in this enzyme that leads to the lysosomal accumulation of glucosylceramide found in Gaucher's disease. Another enzyme is found in the cytosol, i.e., a non-lysosomal environment, that also hydrolyses glucosylceramide, is not deficient in Gaucher's disease and has been termed "glucosylceramidase" by *Aerts et al.* to distinguish it from the lysosomal glucocerebrosidase. *Aerts et al.* describe further that the activity of the non-lysosomal enzyme contributes to the pathology seen in Gaucher's disease and that a combination on their enzyme inhibitor with the spacer and large hydrophobic moiety and glucocerebrosidase enzyme (to restore lysosomal enzyme levels) may be an effective therapy for treatment as defined in Claim 16. This different enzyme approach of *Aerts et al.* has also been published by *Aerts* and his colleagues, *Overkleeft et al.*, "Generation of Specific Deoxynojirimycin-type Inhibitors of Non-lysosomal Glucosylceramidase", *J. Biol. Chem.*, Vol. 273, No. 41, pp. 26522-26527, October 9, 1998. A copy of said publication (JBC Online) is enclosed herewith for the information and convenience of the Examiner. It should be noted that the specially designed inhibitors shown in Fig. 1 of Overkleeft et al. are the identical inhibitors disclosed in the *Aerts et al.* reference with the spacer and large hydrophobic moiety.

Thus, the rationale of Claim 16 of *Aerts et al.* is based on the potent inhibition of the non-lysosomal glucoceramidase and is not based on a strategy that combines a reduction in substrate with supplementated enzyme.

- Sixthly, applicant calls the Examiner's attention to the scientific results shown in the publication by Priestman et al., *Glycobiology* 10, iv, a copy of which is enclosed herewith for the information and convenience of the Examiner. As seen from this publication, N-butyl-deoxynojirimycin (NB-DNJ) is a potent, competitive and reversible inhibitor of ceramide glucosyl-transferase. Using isolate enzyme, the concentration required to inhibit 50% of the enzyme

activity, referred to as the IC50 value, is 20.4 μM. NB-DNJ is also a reversible and competitive inhibitor of glucocerebrosidase. However, when the kinetic parameters of NB-DNJ are measured using isolated, purified human placental β-glucocerebrosidase the IC50 value is 520 μM. Similar data have been obtained using the pharmaceutical form of glucocerebrosidase, Ceredase. Thus, under equivalent conditions *in vitro*, the concentration of NB-DNJ required to inhibit β-glucocerebrosidase is 25 fold higher than observed for inhibiting the ceramide glucosyltransferase (i.e., 520 μM = 25 x 20.4 μM).

These inhibitory results are also shown in Example II at page 14 of applicant's disclosure.

However, as pointed out by Priestman et al., *in vivo* co-administration of NB-DNJ and glucocerebrosidase could lead to inhibition of enzyme activity and compromise combination therapy. It was therefore important to determine the kinetics of infused enzyme in mice treated with NB-DNJ. When mice were thus treated, modest but not statistically significant increases in glucocerebrosidase activity and circulatory half-life were observed. This also demonstrates that *in vivo* co-administration has a synergistic effect and that lower doses of either glucocerebrosidase enzyme or NB-DNJ inhibitor can be used than otherwise required to obtain equivalent inhibition by monotherapy. It is also seen from data provided in the present application in Table 3, page 15, that infused β-glucocerebrosidase activity was not inhibited in the presence of NB-DNJ administered to mice, and that the circulatory half-life of the enzyme was similar to previously published values. These results are unexpected when considered in the light of the teachings of *Aerts et al.* and support the unobviousness of the claimed drug combination.

In view of the foregoing, it is respectfully submitted that applicant's claimed invention is not anticipated by *Aerts et al.* and, therefore, the rejection of Claims 1-3 and 6-7 under 35 U.S.C. §102(b) should be withdrawn.

Claim Rejections - 35 U.S.C. §103

(A) Claims 1-3 and 6-9 have been rejected under 35 U.S.C. §103(a) as being unpatentable over *Platt et al.* (U.S. Patent 5,798,366) in view of *Shorr et al.* (U.S. Patent 5,705,153).

This rejection is traversed for reasons as follows:

In this rejection, the Examiner has cited the separate teachings of:

(1) *Platt et al.* on the use of the N-alkyl DNJs for treatment of Gaucher's disease, and

(2) *Shorr et al.* on the use of a conjugate of glucocerebrosidase and polyethylene glycol (PEG) and similar such polymeric materials for treatment of Gaucher's disease.

Even though conceding that *Platt et al.* does not disclose treatment with "both" of the two drugs recited in applicant's claims, the Examiner states that their combined use "would have been obvious."

It is respectfully submitted that this conclusion is based on hindsight analysis in which the Examiner has reasoned that the claimed method is "no more than the additive effect of two well-known ingredients used in the art for the same purpose." This hindsight analysis is improper as a basis of obviousness, first of all, because there is no motivation in either reference to combine the two types of drugs in a given treatment of Gaucher's disease. The motivation, if any, is found only in applicant's disclosure, not in the references themselves. As stated by the Court of Appeals for the Federal Circuit:

> "Combining prior art references without evidence of such a suggestion, teaching or motivation simply takes

> the inventor's disclosure as a blueprint for piecing together the prior art to defeat patentability." *Ecolochem Inc. v. Southern California Edison*, 56 USPQ2d 1065, 1073 (Fed. Cir. 2000).

Secondly, applicant's disclosed invention does not reside in mere expected effects. Instead, applicant specifically teaches unexpected improved effects at page 3 of the disclosure:

> "By use of the combination drug therapy of the invention, the medical benefits of both types of drugs should accrue to the patients with *reduced amounts of either or both drugs than otherwise necessary to obtain equivalent or enhanced therapeutic results.* That is, an additive or synergistic effect can *reduce the frequency of administration* of the glucocerebrosidase enzyme and *lower the dose* of the long-chain N-alkyl-DNJ otherwise required for monotherapy of the disease (emphasis added)."

Thirdly, the hindsight analysis of the Examiner is contrary to what would be expected from the prior art. Thus, the *Aerts et al.* reference (applied in the previous rejection under §102), states that there would be serious interference by the N-alkyl DNJs with enzyme therapy of patients. That is, co-administration of N-alkyl DNJ and glucocerebrosidase could generate an unwanted, inactive form of the enzyme because of high circulating initial levels of inhibitor. There are no published data that reveal the kinetics and time required to dissociate the enzyme and inhibitor complex, and it is quite possible that considerable losses of glucocerebrosidase activity occur at compound concentrations required to reduce ceramide-specific glucosyltransferase activity *in vivo*. Therefore, it is not obvious that the co-administration of an inhibitor (N-alkyl DNJ) and an enzyme (glucocerebrosidase) would be an effective therapy for the treatment of Gaucher's disease, instead, quite the opposite result would be expected by inducing glycolipid storage. Prior art which strongly suggests that doing what the reference tries to avoid would produce unacceptable results is the very "antithesis of obviousness." *In re Buehler*, 515 F.2d 1134, 185 USPQ 781, 786, 787 (CCPA 1975).

In view of the foregoing, it is respectfully submitted that the claimed invention is not prima facie obvious to one of ordinary skill in the art at the time the invention

was made. Accordingly, the rejection of Claims 1-3 and 6-9 under 35 U.S.C. §103(a) as being unpatentable over *Platt et al.* in view of *Shorr et al.* should be withdrawn.

(B) In a further rejection, Claims 1, 4, 5 and 8-13 have been rejected under 35 U.S.C. §103(a) as being unpatentable over *Platt et al.* (supra) in view of *Legler et al., Biol. Chem. Hoppe-Seyler* 1985) 366(12), 1113-22, and further in view of *Shorr et al.* (*supra*).

In this rejection the Examiner applies the same two references, *Platt et al.* and *Shorr et al.*, as applied in the first rejection (A, above) under §103, but in combination with a third reference, *Legler et al.* This rejection is traversed for reasons as follows:

First of all, Claims 10-13 have been cancelled, and the above argument in traverse of the rejection of claims based on *Platt et al.* and *Shorr et al.* is likewise applicable and is herewith applied in traverse of this second rejection (B) under §103.

Secondly, the *Legler et al.* reference measured inhibitory activity of long chain N-alkyl derivatives of DNJ (N-nonyl- and N-decyl-DNJ) towards glucosylceramidase. However, there is nothing in *Legler et al.*, which suggests that the N-nonyl- or N-decyl-DNJ would be useful for treatment of a glycolipid storage disease such as Gaucher's disease, particularly in combination with glucocerebrosidase. Thus, no data are presented by *Legler et al.* where the compounds have an initial inhibition of ceramide-specific glucosyltransferase. Without this additional effect, these compounds would induce rather than inhibit Gaucher's disease if used therapeutically. The non-lysosomal glucosyltransferase (see Figs. 2-4 and page 12 of applicant's disclosure) is not to be confused with the lysosomal glucosylceramidase as described by *Legler et al.*

Thirdly, applicant calls the Examiner's attention to the scientific results shown in the publication by *Priestman et al.*, 2000, *Glycobiology* 10, iv, a copy of which is enclosed herewith for the convenience of the Examiner. N-Butyldeoxynojirimycin (NB-DNJ) is a potent, competitive and reversible inhibitor of ceramide glucosyl-transferase. Using isolate enzyme concentration required to inhibit 50% of the

enzyme activity, referred to as the IC50 value, is 20.4 μM. NB-DNJ is also a reversible and competitive inhibitor of glucocerebrosidase. However, when the kinetic parameters of NB-DNJ are measured using isolated, purified human placental β-glucocerebrosidase the IC50 value is 520 μM. Similar data have been obtained using the pharmaceutical form of glucocerebrosidase, Ceredase. Thus, under equivalent conditions *in vitro*, the concentration of NB-DNJ required to inhibit β-glucocerebrosidase is 25 fold higher than that observed for inhibiting the ceramide glucosyltransferase (i.e., 520 μM = 25 x 20.4 μM).

However, as pointed out by *Priestman et al.*, *in vivo* co-administration of NB-DNJ and glucocerebrosidase could lead to inhibition of enzyme activity and compromise potential combination therapy. It was therefore important to determine the kinetics of infused enzyme in mice treated with NB-DNJ. When mice were thus treated, modest but not statistically significant increases in glucocerebrosidase activity and circulatory half life were observed. This also demonstrates that *in vivo* co-administration can have a synergistic effect and that lower doses of either enzyme or inhibitor can be used.

In view of the foregoing, it is respectfully submitted that the claimed invention is not *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, particularly in view of the foregoing results published by *Priestman et al.* which support applicant's invention. Accordingly, the rejection of Claims 1,4, 5 and 8-9 under 35 U.S.C. §103(a) as being unpatentable over *Platt et al.* in view of *Legler et al.* and further in view of *Shorr et al.* should be withdrawn.

Double Patenting

Two double patenting rejections have been entered as follows:

Claims 1-9 have been provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of Claims 1-8 of co-pending Application No. 10/054,802; and

(2) Claims 1-8 have been provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable

over Claims 1-3, 10, 11, 14, 15, 25-27, 33-35 and 38 of co-pending Application No. 10/042,527.

These two double patenting rejections are traversed for reasons as follows:

Applicant's claims have been amended to recite the "use" of the combination of drugs for the "preparation of a medicament". That is, the claims recite a method of preparation of a medicament rather than a method of treatment with a medicament. Neither Application Ser. No. 10/054,802 nor Application Ser. No. 10/042,527 claims a use for the preparation of a medicament. Therefore, no double patenting exists and both provisional rejections should be withdrawn.

Nevertheless, applicant offers to file terminal disclaimers in the event that either or both said double rejections are maintained.

Respectfully submitted,

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SJM/mrr
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Encl.